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Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer Practice Guideline Report #2-15

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Report Date: December 5, 2003

SUMMARY

Guideline Question

Is there a role for the use of oral capecitabine (Xeloda™) in the first-line treatment of patients with metastatic colorectal cancer where monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is favoured? Survival was the primary outcome of interest, and time to progression and tumour response were secondary outcomes.

Target Population

These recommendations apply to adult patients with metastatic colorectal cancer, who have not received prior chemotherapy for metastatic disease, in whom monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is favoured. For patients who are at a high risk following curative resection and who received adjuvant chemotherapy, adjuvant treatment should have been completed at least six months prior to being diagnosed with metastatic disease.

Recommendations

- In appropriate patients, standard combination chemotherapy consists of infusional 5-fluorouracil plus leucovorin calcium with either irinotecan or oxaliplatin (refer to the Program in Evidence-based Care's Practice Guideline #2-16b: *Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-fluorouracil and Leucovorin (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer*, and Practice Guideline #2-22: *Oxaliplatin Combined with 5-fluorouracil and Folinic Acid in Advanced Colorectal Cancer [in progress]*).
- If infusion therapy with 5-fluorouracil plus leucovorin calcium with either irinotecan or oxaliplatin is not reasonable, then treatment using oral capecitabine is appropriate.
- The standard dose for capecitabine is 2500 mg/m²/day in two divided doses for 14 days every three weeks. See Appendix 1 for dosing and dose adjustment information.

Qualifying Statements

- Monotherapy with fluoropyrimidines (e.g. 5-FU, capecitabine) or other thymidylate synthase inhibitors (e.g. raltitrexed, pemetrexed) may be favoured in patients with prior pelvic radiotherapy, elevated liver enzymes, age greater than 65 years, ECOG performance status ≤ 1 , and those with an LDH above the upper limit normal. This may also include patients who prefer to avoid intravenous therapy, where travel to a chemotherapy unit would be difficult, or who live in remote locations where an infusional pump program is not available, or in whom placement of a central line catheter is contraindicated. It is also an option for patients with concerns about the toxicity profile of combination chemotherapy (such as hair loss or risk of toxic death), or for whom there is insufficient data regarding the use of combination chemotherapy, or in those subgroups of patients for whom there is no clear survival benefit over single agent anti-thymidylate synthase therapy.
- Preliminary data from a subgroup analysis suggest that capecitabine may be the preferred treatment for patients who had received prior adjuvant therapy at least six months earlier with 5-fluorouracil plus leucovorin, while either capecitabine or 5-fluorouracil plus leucovorin therapy is reasonable for patients who have never received adjuvant therapy. Further trials are needed to confirm this observation.
- The decision to use capecitabine may be influenced by its toxicity. While capecitabine is associated with a lower incidence of stomatitis, alopecia, and neutropenia compared with 5-fluorouracil plus leucovorin, the incidence of hand-foot syndrome is considerably higher with capecitabine.
- Using capecitabine will require dose adjustments in patients with a creatinine clearance less than 60%. This is particularly important in thin elderly patients in whom reductions in creatinine clearance are not adequately reflected in the serum creatinine level alone.
- Where there is hyperbilirubinemia with bilirubin values exceeding 1.5 times normal, it has been recommended that capecitabine treatment be interrupted until the bilirubin drops below the 1.5 times normal value.

Methods

Entries to the MEDLINE (1990 through June (week 3) 2003), CANCERLIT (1990 through October 2002) and Cochrane Library (2003, Issue 2) databases and abstracts published in the proceedings of the 1998 to 2003 annual meetings of the American Society of Clinical Oncology were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which is comprised of medical and radiation oncologists, surgeons, a pathologist, and patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of a periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Two randomized phase III trials demonstrate that single-agent capecitabine administered orally yields higher response rates than 5-fluorouracil plus leucovorin. Pooled response rates were 26% with capecitabine versus 17% with 5-fluorouracil plus leucovorin ($p < 0.0002$)

in a meta-analysis of both trials that has been published in abstract form. Similar median time to progression and median duration of survival was observed with capecitabine and 5-fluorouracil plus leucovorin.

- In the subgroup of patients who relapsed more than six months after completing adjuvant therapy with 5-fluorouracil and leucovorin, capecitabine was associated with higher response rates compared with re-treatment with 5-fluorouracil plus leucovorin. Pooled response rates were 21% with capecitabine versus 9% with 5-fluorouracil plus leucovorin in this subgroup of patients (p-value not reported).
- Capecitabine appears to have a lower incidence of stomatitis, alopecia, and neutropenia compared with 5-fluorouracil and leucovorin. There is, however, a considerably higher incidence of hand-foot syndrome with capecitabine.

Treatment Alternatives

In addition to capecitabine, the following treatment alternatives for first-line therapy exist: 5-fluorouracil plus leucovorin, raltitrexed, irinotecan combined with 5-fluorouracil plus leucovorin, and oxaliplatin combined with 5-fluorouracil plus leucovorin. As always, the choice of treatment should be based on the various system factors, patient preferences, and convenience.

Future Research

A study of capecitabine as adjuvant therapy is ongoing (X-ACT trial). Other studies, utilizing capecitabine as a substitute for infusional 5-fluorouracil, are under development. Studies of capecitabine in combination with other agents, such as irinotecan and oxaliplatin, are under consideration. Some of these treatments may be more beneficial than monotherapy for certain patient subgroups, such as the elderly and the frail.

In another guideline (Practice Guideline #2-22: *Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in Advanced Colorectal Cancer [in progress]*), there is discussion of the recommended way to administer 5-fluorouracil in combination with irinotecan or oxaliplatin. The evidence now demonstrates that when 5-fluorouracil is to be used, it is best administered via a longer infusion rather than short daily intravenous boluses. This method of administration is both superior in terms of tumour response, and more importantly, in reducing certain toxicities. Capecitabine is an oral agent converted to an active 5-fluorouracil metabolite. As a daily, low-dose, oral therapy, it mimics infusional 5-fluorouracil in many respects, including the higher tumour response rates and lower toxicity profile. There is now significant ongoing research activity to assess the role of capecitabine as a replacement for 5-fluorouracil in the combination regimens with oxaliplatin and irinotecan in both the advanced and adjuvant settings. Similarly there is research ongoing to use capecitabine as a substitute for infusional 5-fluorouracil with concurrent radiotherapy for locally advanced or resected rectal adenocarcinoma.

One important area of interest for capecitabine is for frail and elderly patients who are generally not candidates for typical colorectal cancer trials. As this population is underrepresented in trials, it is not possible to adequately assess the risks and benefits of any regimen for these patients. Although capecitabine offers an alternative to intravenous chemotherapy and a generally favourable toxicity profile, it is still associated with important toxicities that impair quality of life and lead to dose adjustments in up to 40% of patients. Research is ongoing to determine the effect of beginning capecitabine at a lower dose, the dose to which many patients are eventually adjusted.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report:

- #2-16: *Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma.*
- #2-16b: *Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-fluorouracil and Leucovorin (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer*

- #2-17: *Use of Raltitrexed (Tomudex™) in the Management of Metastatic Colorectal Cancer.*
- #2-18: *Management of Advanced Colorectal Cancer.* [future topic]
- #2-22: *Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in Advanced Colorectal Cancer.* [in progress]

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*The Practice Guidelines Initiative is sponsored by:
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report is submitted for formal approval to the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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